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EDITORIAL

Pay attention to the application of indocyanine green fluorescence imaging technology in laparoscopic liver cancer resection

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Abstract

Traditional laparoscopic liver cancer resection faces challenges, such as difficulties in tumor localization and accurate marking of liver segments, as well as the inability to provide real-time intraoperative navigation. This approach falls short of meeting the demands for precise and anatomical liver resection. The introduction of fluorescence imaging technology, particularly indocyanine green, has demonstrated significant advantages in visualizing bile ducts, tumor localization, segment staining, microscopic lesion display, margin examination, and lymph node visualization. This technology addresses the inherent limitations of traditional laparoscopy, which lacks direct tactile feedback, and is increasingly becoming the standard in laparoscopic procedures. Guided by fluorescence imaging technology, laparoscopic liver cancer resection is poised to become the predominant technique for liver tumor removal, enhancing the accuracy, safety and efficiency of the procedure.

Key Words: Indocyanine green; Fluorescence imaging technology; Laparoscopy; Hepatectomy; Liver tumor

Core Tip: Fluorescence laparoscopic liver cancer resection, such as indocyanine green (ICG) fluorescence imaging, offers various advantages including visualizing bile ducts, tumor localization, staining of liver segments, detection of microscopic lesions, assessment of resection margins, and visualization of lymph nodes. This technology addresses the lack of direct tactile feedback in traditional laparoscopy and is becoming the standard in laparoscopic procedures. Fluorescence imaging in guiding laparoscopic liver cancer resection is expected to enhance the accuracy, safety and efficiency of the procedure. However, caution is advised regarding potential drawbacks of ICG fluorescence imaging such as false-positive liver staining and limited tissue penetration.

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INTRODUCTION

The treatment model for primary liver cancer has evolved significantly with the advent of targeted therapy and immunotherapy. Some patients in intermediate and advanced stages now have the opportunity for radical surgical resection through conversion therapy, expanding the scope of liver cancer surgery indications[1]. This has made the conditions faced by surgeons more complex, requiring higher precision in surgical damage control and resection[2]. Traditional laparoscopic liver cancer resection has technical limitations, such as difficulty in tumor localization and segment marking, hindering real-time intraoperative navigation[3]. These inherent flaws may result in positive resection margins, preventing radical cure and contradicting the increasingly valued concept of precision liver resection[4].

The emergence of fluorescence laparoscopy technology, particularly indocyanine green (ICG) fluorescence imaging, has effectively addressed the limitations of traditional laparoscopic liver cancer resection[5]. Aoki *et al*[6] first reported on laparoscopic liver cancer resection guided by ICG fluorescence in 2008, sparking global interest in using fluorescence laparoscopy for laparoscopic liver cancer resection[7,8]. This technology combines functional imaging and laparoscopic surgery, offering significant benefits in tumor localization, liver segment marking, and intraoperative navigation[9]. Over the past decade, the application of fluorescence imaging in laparoscopic liver cancer resection has become increasingly refined[10]. Kokudo *et al*[11] suggest that fluorescence imaging represents one of the major technological advances in liver surgery over the last two decades.

PRINCIPLES OF FLUORESCENCE IMAGING

When a substance is irradiated by incident light of a specific wavelength, it absorbs light energy and enters an excited state, immediately de-exciting and emitting emergent light. This emergent light, known as fluorescence, is generated with the incident light typically referred to as the excitation light source[12]. Common excitation light sources include ultraviolet light, visible light, infrared light, and x-ray micro-computed tomography (CT). Luminescent substances used as probe molecules include melatonin, histone deacetylase and glutathione[13]. ICG, a water-soluble molecule with fluorescent dye properties, binds to high-molecular-weight proteins like albumin and lipoproteins in plasma and bile without altering their structure, providing good intravascular stability. Intravenous injection of ICG does not elicit toxic reactions in the body, maintaining effective concentration levels even with low-dose administration[14]. Experimental studies have demonstrated that when excited by light of 750 nm–810 nm, ICG molecules emit fluorescence with a peak wavelength of 840 nm. This fluorescence falls within the window limit of the deep red and near-infrared spectrum, with a wavelength of approximately 10 mm. Utilizing an interference filter lens on a camera, the fluorescence emitted by ICG in deep tissues 10 mm from the surface can be captured, enabling the extraction of signals and the formation of a fluorescence image[15].

Studies have demonstrated that following intravenous injection of ICG into the systemic circulation, hepatocytes take up ICG molecules through their active transport system, leading to secretion into the biliary system and subsequent drainage into the intestines. Notably, there is no enterohepatic circulation. While normal liver tissue can effectively clear ICG within 12 hours–24 hours, patients with cirrhosis exhibit reduced clearance ability[16]. Research has indicated that hepatocellular carcinoma with differentiation retains the capacity to uptake ICG; however, the lack of normal bile duct structure in these cases results in ICG accumulation within the tumor tissue. In contrast, poorly differentiated or metastatic liver cancer cells may impede ICG secretion from adjacent liver tissue, leading to ICG retention in local tissues [17]. Consequently, tissues or fluids containing ICG often exhibit green fluorescence during fluorescence laparoscopy, creating a distinct visual contrast with the red color of normal liver tissue in laparoscopic fusion images.

ICG FLUOROSCOPY IN LAPAROSCOPIC HEPATOCELLULAR CARCINOMA RESECTION

Intraoperative display and examination of the biliary system

The prevention of bile duct injury during laparoscopic liver resection and timely detection of bile leakage during surgery are crucial for preventing and treating complications of laparoscopic liver cancer resection[18]. ICG has a unique advantage in visualizing and examining the biliary system due to its excretion through the biliary tract[19]. The fluorescence produced when ICG-laden bile flows through the biliary system allows for clear visualization of the biliary system, reducing the risk of intraoperative bile duct damage by aiding in the identification of the biliary system and preventing inadvertent injuries[20]. Additionally, in cases of bile leakage during surgery, the fluorescence of leaked ICG can more sensitively pinpoint the location of the leakage compared to traditional bile staining[21]. Real-time ICG fluorescence imaging can assist in identifying variant bile ducts during surgery, offering a level of detail comparable to preoperative magnetic resonance imaging (MRI) and enhancing surgical safety[22]. In summary, the implementation of ICG fluorescence imaging can identify intraoperative biliary variations, thereby helping to prevent complications such as biliary injury and bile leakage[23,24].

Tumor staining for primary liver cancer

The accurate localization of tumor boundaries during laparoscopic liver cancer resection has long been a challenge. ICG fluorescence imaging capitalizes on the differential absorption and excretion of ICG between tumors and normal liver tissue to precisely stain liver tumors with fluorescence[25]. This technique aids in the precise positioning and navigation of tumor resection, enhancing surgical efficiency and minimizing the risk of positive resection margins. The application of fluorescence imaging is particularly prominent in laparoscopic liver resection[26]. Despite advances in imaging techniques such as CT and MRI, approximately 7% of liver tumors remain difficult to detect preoperatively. ICG fluorescence imaging demonstrates high sensitivity for small lesions, detecting lesions as small as 2 mm and addressing the issue of missed diagnoses associated with traditional imaging methods[27]. Research by Kose *et al*[28] showed that intraoperative ultrasound had a 89% recognition rate for superficial liver tumors, whereas ICG fluorescence imaging achieved a recognition rate of 95%. Furthermore, ICG fluorescence imaging can reveal lesions that are undetectable by preoperative MRI or intraoperative ultrasound. The staining patterns observed during ICG fluorescence imaging can provide initial insights into the nature of the tumor[29]. Different tumor properties manifest in distinct staining patterns, such as whole-tumor fluorescence for well-differentiated hepatocellular carcinoma, partial fluorescence for moderately differentiated hepatocellular carcinoma, and ring fluorescence for poorly differentiated hepatocellular carcinoma or metastatic tumor[30].

Laparoscopic anatomical hepatectomy with staining of liver segments

Anatomical liver resection is currently considered to offer a better clinical prognosis for treating malignant tumors that spread along the portal venous system[31]. In the past, liver segment marking relied on the surgeon's subjective estimation of liver segment boundaries based on experience and traditional imaging, rather than true anatomical resection[32]. ICG fluorescence can accurately visualize liver segments and subsegments, offering advantages over traditional labeling methods[33]. ICG is quickly absorbed by hepatocytes after entering the liver through peripheral or portal vein puncture, leading to a significant color difference between stained and unstained liver segments. This clear boundary formation enables real-time navigation of liver dissection boundaries even within the liver parenchyma[34].

Other applications

ICG can flow through lymphatic vessels and attach to proteins within these vessels, becoming concentrated in lymph nodes for identification, aiding in lymphatic dissection for tumors like cholangiocarcinoma[35]. Moreover, ICG fluorescence can also assist in determining the presence of any remaining tumor at the margin of liver resection, thus enhancing the rate of achieving R0 tumor resection[36]. Consequently, it is suggested that liver cancer patients undergoing ICG fluorescence laparoscopic resection may experience improved survival outcomes compared to those undergoing conventional laparoscopic surgery[37].

DEFECTS IN ICG FLUOROSCOPY IN LAPAROSCOPIC HEPATOCELLULAR CARCINOMA RESECTION

ICG fluorescence laparoscopy for cutting edge problems

The staining of tumors with ICG is thought to be due to the tumor compressing the surrounding normal liver tissue, leading to decreased excretion of ICG and its accumulation around the tumor. The fluorescence boundary is expected to be larger than the tumor boundary[18], suggesting that resection beyond the fluorescence boundary is necessary for R0 resection[38]. However, a recent study[39] indicated that, in hepatocellular carcinoma, the pathological border closely aligned with the fluorescent border, requiring a resection margin of 1.5 cm–2.0 cm from the tumor edge for ideal resection. This study suggested resecting the tumor along the fluorescent border, acknowledging that absolute safety could not be guaranteed. We have only one chance to delineate fluorescence for the perfusion region because the liver absorbs ICG. Vigilance is essential when using ICG fluorescence imaging to guide laparoscopic liver cancer resection, and adjusting the resection margin in real-time with intraoperative ultrasound can help reduce the risk of tumor rupture and positive resection margins.

The problem of false positives in ICG fluorescence laparoscopy

The sensitivity of ICG fluorescence to liver lesions can lead to false positives, where additional stained areas may appear during surgery that are later confirmed to be normal liver tissue[27]. Studies have shown that the median false-positive rate for detecting tumors with ICG fluorescence imaging can be as high as 10.5%[40], with even higher rates in patients with liver cirrhosis[29]. Therefore, it is important to carefully assess the timing and dosage of ICG based on the patient's liver condition before surgery, and to approach each stained lesion during surgery with caution using a combination of visual observation, palpation and other imaging techniques.

Limited tissue penetration of ICG fluorescence

The tissue penetration of ICG fluorescence is usually only 8 mm–10 mm, although this depth of penetration already exceeds that of many other probe molecules. Densitometry of ICG fluorescence images is based on the assessment of fluorescent areas by adjusting the threshold of fluorescence intensity, which is insufficient for the penetration of deep tumors in the liver. Therefore, ICG fluorescence staining is still unfavorable for the exploration of deep tumors in the liver [41]. A systematic review[27] highlighted that the sensitivity of ICG fluorescence for tumors deeper than 8 mm ranges from 71% to 79%. Therefore, it is crucial to complement ICG fluorescence imaging with preoperative imaging or intraoperative ultrasound to prevent overlooking deep liver tumor lesions.

CONCLUSION

The continuous advancement of fluorescence imaging technology is enabling the integration of high-end features such as ultra-high definition, large depth of field, high dynamics, wide color gamut, and intelligent adjustment in fluorescence laparoscopy. This progress is expected to drive significant growth in fluorescence laparoscopy. It is anticipated that the technical capabilities of fluorescence laparoscopy will soon match or even surpass those of the current predominant white light laparoscopy, positioning fluorescence laparoscopy as the future standard in laparoscopy. The benefits of fluorescent imaging in tumor staining, liver segment staining, and real-time intraoperative navigation, mean that laparoscopic liver cancer resection guided by fluorescent imaging is poised to become the leading technique for liver tumor resection. This advancement will enhance the precision, safety and efficiency of laparoscopic liver cancer resection.

FOOTNOTES

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